

Anthrax Vaccine Adsorbed (AVA) Safety Studies Since 2008

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AVA Safety Data

- Post-licensure VAERS data
 - Publications post-2008
 - Unpublished
- Studies using other data sources
 - Publications post-2008

POSTLICENSURE VAERS DATA

Vaccine Adverse Event Reporting System (VAERS)

- ❑ **National spontaneous (or passive) reporting system for AEs after US-licensed vaccines**
 - Receives \approx 40,000 reports annually*
 - Accepts reports from healthcare providers, manufacturers, and public
 - Signs/symptoms of AE are coded using the Medical Dictionary for Regulatory Activities (MedDRA)** terms and entered into a database
 - Primarily for signal detection and hypothesis generation
- ❑ **Jointly administered by CDC and FDA since 1990**

* 2012-2016

** <http://www.meddra.org/>

Objectives of VAERS

- ❑ **Signal detection/hypothesis generation**
 - Detect new, unusual, or rare vaccine AEs
 - Identify potential risk factors in vaccine recipients for particular types of AEs
 - Monitor trends in known AEs, particularly increases
 - Identify vaccine lots with increased numbers or types of reported AEs (FDA lead)
- ❑ **Enable rapid response to vaccine safety concerns or public health emergencies**

VAERS

- ❑ Adverse events are temporally associated events which might be caused by a vaccine or might be coincidental and not related to vaccination
- ❑ VAERS data must be interpreted with caution and cannot generally be used to assess causality
- ❑ In recent years (2011 – 2014) , there were ~ 30,000 VAERS reports per year; 7% classified as serious

VAERS

- ❑ **VAERS reports are classified as “serious” if they contain information that the AE resulted in**
 - death
 - hospitalization
 - prolongation of hospitalization
 - life-threatening illness
 - persistent or significant disability
 - congenital anomalies

VAERS Strengths and Limitations

Strengths

- ❑ National data; accepts reports from anyone
- ❑ Rapid signal detection
- ❑ Can detect rare AEs
- ❑ Collects information about vaccine, characteristics of vaccinee, and AEs*
- ❑ Data available to public

Limitations

- ❑ Reporting bias
- ❑ Inconsistent data quality and completeness
- ❑ Lack of unvaccinated comparison group
- ❑ Generally cannot assess if vaccine caused an AE
- ❑ Pregnancy inconsistently reported

*Some reports have no adverse event

Adverse Events Reported to VAERS Following AVA (1 of 2 slides)

- ❑ Review of deaths and other serious reports following AVA receipt
- ❑ VAERS reports from August 16, 2005 through January 16, 2007
 - 4753 filed
 - 4273 (90%) nonserious
 - 455 (9.6%) serious
 - 25 (0.5%) deaths

Adverse Events Reported to VAERS Following AVA (2 of 2 slides)

❑ Most commonly reported non-fatal serious conditions*

- Myalgia (39%)
- Depression (26%)
- Arthralgia (35%)
- Asthenia (25%)
- Pain (29%)
- Rash, anxiety, and insomnia (24%)
- Headache (28%)
- Back pain (20%)

❑ Conclusions:

- No serious adverse event definitely linked to AVA vaccination.
- No causal relationship suggested for SAEs or death.

* Not mutually exclusive

Niu MT. *Vaccine*. 2009.

Thrombocytopenia following Vaccines

Reports to VAERS, 1990-2008

- ❑ Record review of thrombocytopenia (TP) (platelets $< 150,000 \times 10^9/\text{ml}$) reports to VAERS July 1990 through December 2008
 - 1510 reports
 - 1440 reports following exclusions
 - 14 reports followed anthrax vaccine
- ❑ **Conclusions:**
 - It may be coincidental

Adverse Events Reported to VAERS Following AVA, 2009-2017 (1 of 2 slides)

- ❑ **VAERS:** From January 1, 2009 through June 30, 2017
- ❑ **2439 nonduplicate reports following AVA receipt**
 - 329 (13.5%) considered serious (i.e., death, hospitalization, or permanent disability)
 - 5 deaths (3 with autopsies): causes of death included cardiovascular disorders, unintentional or intentional injuries, and chronic illnesses
 - 80% in persons < 40 years of age
 - 25% in women and 75% in men
 - 46% received AVA alone

Adverse Events Reported to VAERS Following AVA, 2009-2017 (2 of 2 slides)

- ❑ 1770 MedDRA terms were reported in conjunction with AVA for 2009-2017
- ❑ 10 most common adverse events
 - Headache (14.7%)
 - Injection-site erythema (13.6%)
 - Pain (12.6%)
 - Fever (11.6%)
 - Fatigue (11.5%)
 - Arthralgia (11.2%)
 - Erythema (11.2%)
 - Pain at the injection site (9.9%)
 - Injection site swelling (9.8%)
 - Rash (9.4%)
- ❑ Conclusions: No new safety concerns detected in VAERS monitoring

POSTLICENSURE STUDIES USING OTHER DATA SOURCES

Serious Adverse Events in Studies with AVA, 2008-2016 (1 of 2 slides)

Author	Year	~AVA Doses (recipients x schedule)	Serious Adverse Events	Possibly Related to AVA
Zhang	2008	770	None	None
Rynkiewicz	2011	50	1	None
Hopkins	2013	40	None	None
Ionin	2013	800	None	None
Bernstein	2014	820	None	None

Serious Adverse Events in Studies with AVA, 2008-2016 (2 of 2 slides)

Author	Year	~ AVA Doses (recipients x schedule)	Serious Adverse Events	Possibly Related to AVA
Hopkins	2014	600	2	None
Wright*	2014	8320	231	6 (no deaths)
King	2015	950	None	None
Hopkins	2016	70	None	None

* AVRP

Health-Related Quality of Life following AVA Receipt (1 of 2 slides)

- ❑ **Anthrax Vaccine Research Program (AVRP) Human Clinical Trial**
 - 1562 participants 18 to 61 years of age
- ❑ **Health-related quality of life measured**
 - SF-36 health survey
 - 0, 12, 18, and 42 months after vaccination
- ❑ **Covariates:** study group, dose number, study site, sex, smoking status, and age, race, and body mass index categories and interactions between each of these and dose number.

Health-Related Quality of Life following AVA Receipt (2 of 2 slides)

❑ Outcomes:

- Mean physical and mental scores tended to decrease after baseline
- No difference between the groups, including saline placebo

❑ Conclusion: No association between receipt of AVA and altered quality of life over a 42-month period

AVA Safety in 18- to 20 Year Olds

- ❑ **Reanalysis of convenience sample from 4 previous studies**
- ❑ **Results:**
 - Rates of any elicited local AEs were not significantly different between younger and older age groups for
 - injection site events (79.2% vs. 83.8%, $P = 0.120$)
 - systemic events (45.4% vs. 50.5%, $P = 0.188$)
 - Robust and similar proportions of seroresponses to vaccination were observed in both age groups.
- ❑ **Conclusions:** AVA was safe and immunogenic in 18 to 20 year olds compared to 21 to 29 year olds

Squalene Antibodies in Gulf War Veterans with Multi-symptom Illness (1 of 2 slides)

- ❑ Cohort study of Seabees who served from Sept. 1990 until time of survey in 1994
 - 527 Gulf War veterans
 - 970 non-deployed
- ❑ **Matching / Confounders:** Age group, race/ethnicity, marital status, high school graduation rates similar for
 - Participants and nonparticipants
 - Squalene antibody-positive and squalene antibody-negative veterans
 - Ill and well veterans

Squalene Antibodies in Gulf War Veterans with Multi-symptom Illness (2 of 2 slides)

- ❑ **Outcomes:** Squalene antibodies
 - Were similar in deployed and nondeployed veterans
 - Were not associated with chronic multisystem illness
- ❑ **Conclusions:**
 - No association found between squalene antibody status and chronic multi-symptom illness.

Disability Risk among Army Personnel following AVA Receipt, 1998-2005 (1 of 2 slides)

❑ Cohort study

- December 15, 1997 through February 15, 2005
- 1, 001,546 soldiers; 43.8% with at least 1 dose of AVA

❑ Data source: Total Army Injury and Health Outcomes Database (TAIHOD) and Military Vaccine Agency (MILVAX)

❑ Disabilities assessed:

- | | |
|-------------------|-------------|
| — Musculoskeletal | — Digestive |
| — Neurological | — Cardiac |
| — Respiratory | — Endocrine |
| — Mental | — Other |

Disability Risk among Army Personnel following AVA Receipt, 1998-2005 (2 of 2 slides)

- ❑ **Unadjusted rates**
 - Vaccinated 60/100,000
 - Unvaccinated 178/100,000
- ❑ **Matching / Confounders:** adjusted for race and sex (strong predictors of disability) and stratified by length of service
- ❑ **Results:** dose response observed for soldiers with 2 years of service who entered the Army in 2000 or later; otherwise, an inverse association was observed
- ❑ **Conclusion:** AVA not associated with differences in risk of disability evaluation, disability determination, or reason for disability

Disability among US Army Veterans following AVA Receipt (1 of 2 slides)

❑ Case-control study

- Active duty personnel separated from the US Army
- From December 1, 1997 through December 31, 2005

❑ Data source: TAIHOD, and Veterans Benefit Administration (VBA) Compensation and Pension and Benefits database, and MILVAX

❑ Cases:

- $\geq 10\%$ disabled according to Army (N=5,846)
- or VBA disabled after separation (N=148,934)

❑ Controls:

- Separated without disability and not on VBA disability

Disability among US Army Veterans following AVA Receipt (2 of 2 slides)

- ❑ **Covariates:** age, gender, race, pay grade, hostile fire pay, major command code, ever served abroad.
- ❑ **Results:**
 - After adjustment for covariates, veterans who had been vaccinated against anthrax had lower odds of later receiving VBA benefits than their unvaccinated counterparts
 - There was no association between prior vaccination against anthrax and odds of disability separation from the Army, overall
- ❑ **Conclusion:** Evidence that vaccination against anthrax is not associated with long-term disability

Type 1 Diabetes in Military following AVA receipt, 2002-2008 (1 of 2 slides)

- ❑ **Retrospective population-based cohort**
- ❑ **Data source:** Defense Medical Surveillance System
- ❑ **Active military, 17-35 years of age**
 - 2.3 million individuals followed for 7.6 million person years
 - January 1, 2002 through December 31, 2008
 - Incident diabetes based on ICD-9 codes
 - 1, 074 incident type 1 diabetes cases

Type 1 Diabetes in Military, following AVA receipt, 2002-2008 (2 of 2 slides)

- ❑ **Matching / Confounders:** age, race, sex, service branch, military grade, calendar year, and receipt of one or more of the study vaccines.
- ❑ **Outcome:** RR =1.0 (95% CI, 0.85-1.1) for development of type I diabetes following AVA receipt
- ❑ **Conclusion:** No increased risk for AVA and type 1 diabetes

Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) in the Military following AVA receipt (1 of 2 slides)

- ❑ **Matched case-control study**
- ❑ **Data source:** Defense Medical Surveillance System
 - Inpatient and Outpatient ICD-9 codes for rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE)
- ❑ **Confounders / Covariates:** Matched for sex, age, service branch and controlled for deployment status in multivariable models

Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) in the Military following AVA receipt (2 of 2 slides)

- ❑ **RA and receipt of AVA in prior**
 - 1095 days OR = 1.0 (95% CI, 0.5-2.2)
 - 90 days OR = 3.9 (95% CI, 1.18-14.3)
- ❑ **SLE and ever receipt of AVA** OR = 0.9 (95% CI, 0.3-3.3)
- ❑ **Conclusions:**
 - AVA associated with recent onset but not long term RA
 - No association with the number of doses
 - No association with SLE

Pregnancy and Infant Health Outcomes among Women in Smallpox Vaccine Registry Who Received AVA (1 of 2 slides)

- ❑ **Retrospective cohort of women exposed to AVA**
- ❑ **Data source:** National Smallpox Vaccine in Pregnancy Registry (NSVPR)
 - 155 smallpox vaccine (unexposed)
 - 308 AVA & smallpox vaccine (exposed)
- ❑ **Confounders / Covariates:** Study limitation was inability to control for potential confounding.

Pregnancy and Infant Health Outcomes among Women in Smallpox Vaccine Registry Who Received AVA (2 of 2 slides)

- ❑ **Results:** Compared to military women exposed to neither vaccine, both the unexposed and exposed groups had
 - Similar fetal outcomes: ectopic, elective and spontaneous abortions, and stillbirths
 - Similar infant health outcomes: preterm births, low birth weight, mean birth weight, male sex, and major birth defects.
- ❑ **Conclusions:** Similar rates between AVA-exposed and AVA-unexposed groups provide further confidence in safety of AVA when given inadvertently to a relatively young and healthy population during pregnancy

Birth Defects among Infants Born to Military Women Who Received AVA in Pregnancy (1 of 3 slides)

- ❑ Retrospective cohort of infants born to military women from 2003 – 2010
- ❑ Data source: DoD Birth and Infant Health Registry
- ❑ ICD-9 coded birth defects
 - 126,839 live born infants

Birth Defects among Infants Born to Military Women Who Received AVA in Pregnancy (2 of 3 slides)

□ Covariates in multivariable model

— Infant variables

- Birth year
- Infant sex
- Plurality
- Occupation
- Military service branch
- Rank
- Reserve status

— Maternal variables

- Age at delivery
- Race/ethnicity
- Marital status
- Deployment during pregnancy & amount of time deployed
- Other potentially risky vaccinations in first trimester

Birth Defects among Infants Born to Military Women Who Received AVA in Pregnancy (3 of 3 slides)

- ❑ **Results:** After adjustment, AVA receipt during first trimester VS
 - Any other time OR = 1.1 (95% CI, 0.93 – 1.29)
 - Pre-pregnancy OR = 1.05 (95% CI, 0.88 – 1.24)
 - Post-pregnancy OR = 1.17 (95% CI, 0.97 – 1.43)
 - Never OR = 1.03 (95% CI, 0.86 – 1.23)
- ❑ **Conclusions:** No strong associations between AVA vaccination during pregnancy and birth defects risk were observed

ADVERSE EVENTS – SC VERSUS IM ROUTE OF ADMINISTRATION

Dosing Schedule for 2014 AVR P Study

Study Group	# Enrolled	# of AVA doses	Route	Month								(booster) 30	(booster) 42
				0	0.5	1	6	12	18				
8-SC	259	8	SC	AVA	AVA	AVA	AVA	AVA	AVA	AVA	AVA	AVA	
8-IM	262	8	IM	AVA	AVA	AVA	AVA	AVA	AVA	AVA	AVA	AVA	
7-IM	256	7	IM	AVA	S	AVA	AVA	AVA	AVA	AVA	AVA	AVA	
5-IM	258	5	IM	AVA	S	AVA	AVA	S	AVA	S	AVA	AVA	
4-IM	268	4	IM	AVA	S	AVA	AVA	S	S	S	AVA	AVA	
Placebo SC	133	0	SC	S	S	S	S	S	S	S	S	S	
Placebo IM	127	0	IM	S	S	S	S	S	S	S	S	S	

Wright JG, et al. *Vaccine*. 2014

Injection Site Reactions

Adverse Events Significantly Less Likely in IM than SC AVA Recipients

Adverse Event	Female	Overall	Male
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Warmth	0.11 (0.08, 0.14)		0.25 (0.19, 0.33)
Itching		0.19 (0.14, 0.24)	
Erythema	0.14 (0.10, 0.18)		0.29 (0.23, 0.37)
Induration	0.19 (0.15, 0.24)		0.32 (0.25, 0.42)
Edema		0.36 (0.31, 0.43)	
Nodules	0.07 (0.05, 0.09)		0.20 (0.14, 0.28)
Bruise		0.72 (0.52, 0.99)	

Significant increase in reports of arm motion limitation for IM compared to SC [OR = 1.80 (1.37, 2.38)]

Systemic Reactions

- ❑ **Route of administration did not have a significant influence on systemic AE occurrence except for:**
 - Higher occurrence of generalized muscle ache (6.7%) amongst IM recipients compared to SC (5.3%) [OR 1.59 (1.13, 2.23)]
 - Lower occurrence of fatigue among IM recipients (8.6%) compared to SC (10.6%) was observed, but was not significant [OR = 0.80 (0.62, 1.03)]

Conclusions

- ❑ No new safety concerns since December 2008 based on
 - updated VAERS review
 - a review of the published literature
- ❑ Injection site reactions were less common with IM than the SC route of administration

Questions?



The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention

Additional Slides

Birth Defects among Infants Whose Mothers Received AVA in Pregnancy (1 of 3 slides)

- ❑ Retrospective cohort of infants born to military women from 1998 through 2004
- ❑ Data source: DoD Birth and Infant Health Registry
- ❑ ICD-9 coded birth defects
 - 115,169 total infants
 - 37,140 born to ever-vaccinated mothers
 - 3,465 born to mother vaccinated in first trimester; 938 exposed to >1 dose
- ❑ Major birth defect
 - 162/3,465 (4.7%) of first trimester infants
 - 25/663 (3.8%) exposed vaccinated in later trimesters

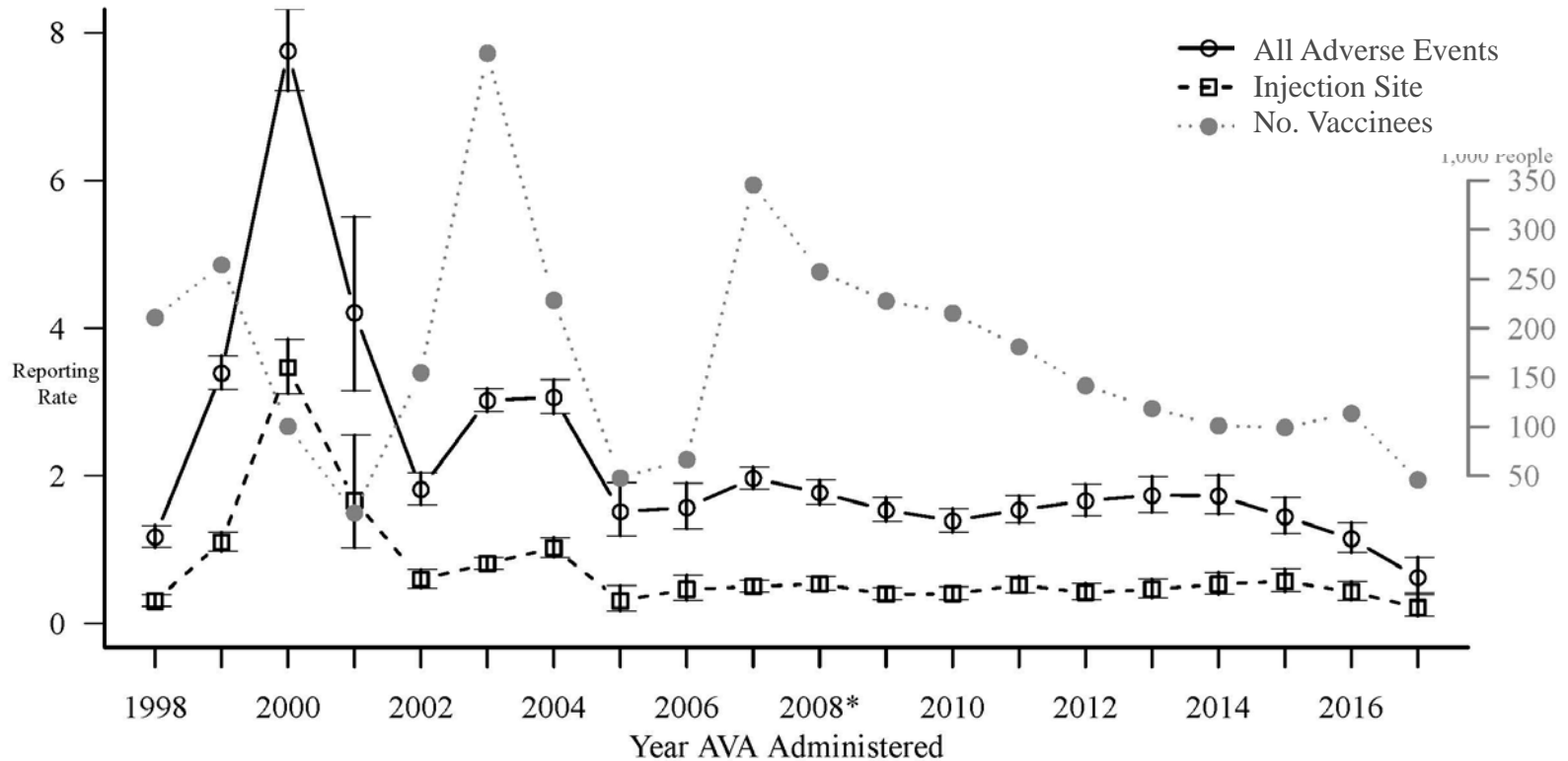
Birth Defects among Infants Whose Mothers Received AVA in Pregnancy (2 of 3 slides)

- ❑ Associations with major defects in multivariable regression analysis: age over 35, male sex, prematurity
- ❑ No association with first trimester vaccination after adjusting for maternal age, gender, and prematurity
 - Infants exposed to first trimester AVA vs infants of women vaccinated outside of the first trimester (OR 1.18, 95% CI 0.997-1.41)
- ❑ **Matching / Confounders:** adjusted for gestational age, birth status, infant gender, maternal age, maternal race, maternal marital status, branch of service, rank, and military status (but not deployment)

Birth Defects among Infants Whose Mothers Received AVA in Pregnancy

- ❑ Adj OR for “Atrial septal defect (ASD)” increased
 - No association if premature infants excluded (ASD difficult to distinguish from patent foramen ovale)
 - No association after adjustment for multiple comparisons
- ❑ **Conclusions:**
 - Overall, no strong or consistent associations were observed between maternal vaccination and specific defects or patterns of defects in infants
 - The degree of association they did see [with ASD] is consistent with the increase observed for “late recognized” pregnancies

Rate of Reports Following AVA per 1,000 People Vaccinated



*Comparing rates before and after year 2008 (route changed late 2008 from SQ to IM): P-value<2.2e-16 (CI (1.83 1.87)) for injection site; P-value<2.2e-16 (CI (1.77 1.87)) for all.